The invention relates to of complexes of the active enantiomer of the ibuprofen (S (+) - ibuprofens) with cyclodextrin, a method to their preparation and their use as pharmaceutical preparation.

S (+) - ibuprofen (S (+) - 2 (- 4-Isobutylphenyl) propionsäure) is a good known medicament with antiinflammatory, antipyretischen and analgetischen properties. S (+) - ibuprofen is a crystalline substance of small water solubility and wettability. Despite this fact ibuprofen becomes relative rapid absorbed and possesses a complete bioavailability after oral ingestion (Albert, K.S., Gernaat, C.M. (1984): Note. J. Med., 77, 40). Various reports shown variations in the absorption velocity solid, oral dosage forms of the ibuprofen (Gillespie, W.R., DiSanto, A.R., Monovich, R.E., Albert, K.S. (1982): J. Pharm. Sci., 71, 1034; Stead, J.A., Freeman, M., John, E. G., Ward, G.T., Whiting, B. (1983): Int. J. Pharm., 14, 59).

The Ibuprofen Razemat becomes in various, available acquisitionable pharmaceutical compositions used (z. B. Brufen (blade), Aktren (Bayer)), although alpha - methyl aryl acetic acid analogues in its pharmacodynamic properties a significant Stereospezifität exhibit, because only S (+) - Enantiomere the Prostaglandinsynthese restrain. Further the stereoselective arrangement of the Enantiomere in synovialer liquid and in the plasma became examined with patients with arthritis. That content of the active S-enantiomer in the synovialen liquid lay to all times with all patients over that of the R-enantiomer, whereby the concentration ratio amounted to S to R 2.1 (Day, R. Williams, K., Graham, G., Lee, E., Knihinicki, R., champion, D. (1988): Clin. Pharmacol. Ther. (Pc. Louis) 43 (5), 480). These observations point to the possibility of a substantial dose decrease of the ibuprofen, whereby the side effects became reduced.

Cyclodextrins are cyclic oligomers of the glucose with apolar inner surfaces, which are in the layer to bind hydrophobic molecules. Cyclodextrins are crystalline, which applies likewise to its complexes with foreign molecules. These complexes show something improved water solubility characteristics compared with the drugs themselves. The latter improvements form the subject-matter of various overview articles and from patents (Szejtli, J., cyclodextrin Technology, Kluwer Academic Publishers, Dordrecht, bad clay/tone, London 1988; Pitha, J., Szente, L., Szejtli, J., Molecular Encapsulation OF Drugs by cyclodextrin and Congeners, in control LED Drug Delivery, (carriage return character) press Inc., (OD. Bridge, S.D.), Boca Raton, flat steel bar, 1983, pp. 125-148).

The complex formation of the racemic ibuprofen and the cyclodextrins became already detailed examined in the literature. A solid racemic Ibuprofen beta - Cyclodextrin complex is producible by various methods. Kurozumi et. aluminium (Kurozumi, M., Nambu, N., Nagai, T. (1975): Chem. one. Pharm. Bulletin. 23 (12) 3062) a provided inclusion compound with various non-steroidal, antiinflammatory drugs including ibuprofens with alpha - and beta - cyclodextrin from an homogeneous solution by coprecipitation and freezing drying procedures ago. It was found that the bioavailability of the prepared products was better compared with the drugs themselves. After Ibuprofengaben could be recovered from the urine 9.7% of the Ibuprofen

beta - Cyclodextrin complex and 5.0% of the free ibuprofen (Nambu, N., Shimoda, M., Takahashi, Y., Ueda, H., Nagai, T. (1978): Chem. one. Pharm. Bulletin. 26 (10) 2952).

The preparation (R, S) - of the Ibuprofen beta - Cyclodextrin complex in a 1:1 molar ratio is described in Japan Kokai JP 80.92.431 (Kakenyaku Kako of cost, Ltd. 1980). Ibuprofen and beta - cyclodextrin aqueous sodium hydroxide solution dissolved became in a 2%igen. After neutralization of the solution with HCl the complex became precipitated. This Ibuprofen beta - Cyclodextrin complex shows smaller disturbances of the mucous membrane diaphragms and a better odor than the pure ibuprofen.

In Japan Kokai JP 81.46.837 (Kowa Pharm. Industry of cost, Ltd., 1981) is a spray drying procedure for the coating of the Ibuprofenteilchen with beta - cyclodextrin described, in order to prevent the bitter taste. 2.0 g ibuprofen, 5.7 g beta - cyclodextrin and 200 ml waters became spray-dried with 80 DEG C mixed and this mixture. The molar ratio of this product amounts to 2 moles ibuprofens on 1 mole beta - cyclodextrin.

Chow et. aluminium (Chow, D.D., Karara A.H. (1986): Int. J. Pharm. 28 95; Chow, D.D. (1986): Diss. Abstr. Int.B 1987, 47 (7) 2858) a provided solid complex by the release from 2x10< - > < 3> M (R, S) - ibuprofens and 16x10< - > < 3> M beta - cyclodextrin in waters ago. The precipitated complex became filtered, washed and dried with 40 DEG C over night. The stoichiometric ratio of of the solid complex amounted to 2:3 (ibuprofen to beta - cyclodextrin), which refers to the contributions of various complexes, which präzipitieren in the system. Bio-availability tests with rats shown that the absorption factor was both for the free and for the komplexierte ibuprofen same. The komplexierte ibuprofen achieved however the point plasma concentration around the 2,5-fache more rapid as the drug alone.

▲ top

Cyclodextrin (R, S) - Ibuprofen complexes became further by Markarian et.al. (Markarian, B.M., Choen, G.L. (1988): Eur.Pat. Appl. EP 274,444) by mixing (R, S) - ibuprofens and a cyclodextrin in a solution with elevated temperatures prepared. The solubility of the ibuprofen was substantially increased.

Also in other publications the influence of cyclodextrins or Cyclodexgrinderivaten on the solubility and diffusion rate of the ibuprofen is described (Nenard, F.A., Dedhiya, M.G., Rhodes, C.T. (1988): Drug. Dev. Ind. Pharm. 14 (11) 1529; Szemán, J. Szente, L., Szabó, T., Szejtli, J.: Proceedings OF the Fourth Int. Symp. on of cyclodextrin, Kluwer Academic Publishers, (Eds.: Huber, O., Szejtli, J.), Dordrecht, 1988 p. 393; Orienti, I., Cavallari, C, Zecchi, V. (1989): Arch. Pharm. (Weinheim) 322,207).

From the EP 0,346,006 pharmaceutical preparing are known, which complexes of the beta - contain of cyclodextrin with Ibuprofensalzen. The use of S (+) - ibuprofens in free form and the use of S (+) - Ibuprofen salts in compound with cyclodextrins described or suggested does not become in this application. The Cyclodextrin ibuprofencomplexes known from the state of the art use without exception the racemic mixtures of the ibuprofen and show the disadvantage that high doses on (R, S) - ibuprofens with the disadvantages used linked thereby to become to have.

It is an object of the invention, new complexes of S (+) - ibuprofen to make available.

This object becomes according to invention dissolved by the fact that an inclusion complex of active S (+) - enantiomer of the ibuprofen and/or its physiological acceptable salts with a cyclodextrin and/or a Cyclodextrinderivat provided becomes. Further a method becomes the preparation of these Cyclodextrin complexes disclosed.

Provided the according to invention complexes from S (+) - ibuprofens and cyclodextrin exhibit a good bioavailability and a better taste, than the complexes of the state of the art.

According to invention the cyclodextrin is a compound of the subsequent formula (I) EMI5.1 how
n = 6.7 or 8
R = H and/or an alkyl radical (c1 - C5), aminoalkyl (c1 - C5), alkyl or dialkyl (c1 - C5) - aminoalkyl (c1 - C5), with exception of the Diethylaminoethylsubstituenten, or a Cyclodextrin etherderivative.

The Cyclodextrinderivat can be a mixed ether. The average number at substituents at the Cyclodextrinring (HP) can lie within the range of 0-21. The ratio of S (+) - ibuprofen to the cyclodextrin lies within the range of 0,01 to 2.00 parts by weight.

The c1 - C5-Alkylgruppe of the formula (I) is unbranched or branched and is a prefered c1 - C3-Alkylgruppe, in particular a prefered methyl, ethyl, Propyl or isopropyl group. The Aminoalkyl and the alkyl or Dialkylaminoalkylgruppen know an unbranched or branched c1 - C5-Alkylgruppe to contain, a prefered c1 - C3-Alkylgruppe, in particular a prefered methyl, ethyl, Propyl or isopropyl group. The Diethylaminoehtylgruppe becomes exclusive used in mixed Cyclodextrin etherderivatives.

The degree of substitution HP of the Cyclodextrinderivate knows within the range of 0 21, in the mixed ethers can HP of the alkyl substituent prefered 0 14 amount to and the sum of the substituents is appropriate for prefered with 0 21.

The Cyclodextrinverbindung knows further a dihydroxylalkyliertes polymer derivative, a water-soluble Cyclodextrinpolymer (Szejtli, J., Zsadon, B., Fenyvesi, E., Szilasi, M., doing DOS, F. (1982) : Hung. Teljes HU 180.597) or an ionic, water-soluble Cyclodextrinpolymer (Szejtli, J., Fenyvesi, E., Zsadon, B., Szilasi, M., Décsei L. (1984): Eur. Pat. Appl. EP 119,453) its. The ionic polymer is a prefered Aminoalkyl (c1 - C3) - or dialkyl (c1 - C3) - aminoalkyl (c1 - C3) - substituted polymer.

The weight ratio of S (+) - ibuprofen and the cyclodextrin lies within the range of 0,01 to 2.0, further prefered between 0,01 and 0,25, between 0,5 to 2.0 and between 0,1 to 0,8; prefered in particular amounts to the ratio from cyclodextrin to S (+) - ibuprofen 1:1.

An other object of the invention is the provision of a method to the preparation of ibuprofens.

Becomes according to invention S (+) - Ibuprofen cyclodextrincomplex by a Phasentransformation prepared, whereby S (+) - ibuprofen in an aqueous suspension of suitable cyclodextrins as landlord molecules molten becomes.

The foreign molecule becomes agitated in an aqueous suspension of the cyclodextrin over its melting point, whereby a crystalline inclusion complex develops. Bottom vigorous agitation becomes the molten foreign molecule in form of small droplets in the Cyclodextrinsuspension dispersed, whereby an emulsion suspension system develops. After 20 - 30 hours is the complexation complete, dependent of the agitating intensity, the sample yardstick, the temperature etc. If the reaction system becomes a simple suspension, the complexation is complete. Subsequent one will the suspension cooled, in order to decrease the solubility of the complex. After the filtration the crystalline complex becomes dried.

Bottom physiological conditions it was found that the water solubility after above method prepared S (+) - Ibuprofen beta - Cyclodextrin complex the ninefold of the nichtkomplexierten ibuprofen exceeds. Further become reduced in this preparation the undesirable odor, taste and the disturbing effect on the mucous membrane diaphragm of the ibuprofen. The good water solubility, the reduced crystallinity and the improved wettability of such a prepared S (+) - Ibuprofen cyclodextrincomplex resulted in better solubility characteristics (table I) and resulted in the possibility of the application of the compound in new pharmaceutical preparing of S (+) - ibuprofens, e.g. in the form of shower tablets, syrups or suspensions.

The method possesses the known subsequent advantages compared with from the state of the art:

No organic solvents used become. Normally organic solvents become used in the reaction mixture, if the complex in an homogeneous solution or a suspension becomes prepared. The volume of the reaction mixture is relative small, because the cyclodextrin is not present

dissolved.
The invention process is very simple (agitation, filtration, drying).
This method can become light industrial conditions performed bottom in large yardstick.
The active substance loss is not only small and it takes place pollution of the environment.
No excess of the foreign molecule required becomes according to invention, as this with the integration procedure by melts necessary is.

In order the good biological availability of S (+) - ibuprofen from the komplexierten form to test, performed became in vitro Diffusionsversuche. The diffusion of S (+) - ibuprofen from the beta - Cyclodextrin complex was more rapid, S (+) - Ibuprofen amount in the receptor cell amounted to the 1,6fache with pH = 1.2 after 6 hours in the comparison to the free drug (table II).

Other prefered embodiments of the invention result also from the lying close claims.

Examples

Example 1

Preparation of S (+) - ibuprofens with an improved water solubility using beta - cyclodextrin to the molecular inclusion

S (+) - Ibuprofen beta - Cyclodextrin complex becomes in a molar ratio from 2 to 3.5 prepared, whereby the 20%ige excess of the beta - cyclodextrin in the reaction mixture the displacement of the balance for inclusion integration facilitated.

A 2000-ml-Dreihalskolben becomes with 1100 ml waters filled and on 60 DEG C in the water bath heated. Bottom vigorous agitation become 55 g (0.27 mol) S (+) - ibuprofens the water added. After molten S (+) - ibuprofens in an emulsion is present, 626 g become beta - cyclodextrin (0.475 mol, moisture content 13.8%) added. The obtained emulsion suspension becomes with 60 DEG C and 600 RPM agitated. In this inclusion procedure entrapped S (+) becomes - ibuprofen analyzed. The complexation is complete within approximately 24 hours. Afterwards the suspension becomes slow cooled on 5 DEG C. The product becomes filtered on a glass filter bottom vacuum. The crystalline complex becomes prolonged dried with 60 DEG C two hours.

S (+) - Ibuprofengehalt of such a prepared product amounts to 9.7 0.25%, the weight loss amounts to approx. 5 - 6 %. The amount at free S (+) - ibuprofens in the prepared complex amounts to about 0.6 - 0.8 g/100g product, certain by the warm setting free analysis. The degradation and the evaporation of S (+) - ibuprofens become in the temperature range of 100 DEG C - 165 DEG C on the TEA curves of free S (+) - ibuprofen and its mixture with beta - cyclodextrin shown (fig 1). The measurable amount of a volatile organic compound from S (+) - Ibuprofen beta - Cyclodextrin complex amounts to only 0.6 - 0.8 mg/g in a temperature range of 100 DEG C to 180 DEG C, whereby the complex formation of S (+) - of ibuprofen confirmed becomes. The complex shows a good solubility and good dissolution characteristics (vgl. Table I).

Example 2

Preparation of molecular entrapped S (+) - Ibuprofen beta - cyclodextrin

55 g (0.27 mol) S (+) - ibuprofens and 626 g (0.75 mol) beta - cyclodextrin waters given reach 500 ml. The reaction mixture becomes prolonged agitated with 60 DEG C with a Ultra Turrax (10,000 RPM) an hour. Subsequent one becomes the suspension on 5 DEG C cooled. The solid product becomes filtered and dried with 60 DEG C.

Example 3

Preparation water solubility using gamma cyclodextrin to the molecular inclusion, improved by S (+) - ibuprofens with

One 1000 ml three-neck pistons become with 400 ml waters filled and in the water bath on 60 DEG C heated. Bottom vigorous agitation become 55 g (0.27 mol) S (+) - ibuprofens the water

given.

After emulsification of the molten ibuprofen 616 g (0.475 mol) become gamma cyclodextrin added. The obtained emulsion suspension becomes with 600 RPM with 60 DEG C agitated. After the inclusion procedure the analysis of the entrapped ibuprofen follows. The complexation is terminated after approximately 24 hours. The suspension becomes subsequent slow cooled on 5 DEG C. The product becomes on a glass filter in vacuo filtered. The crystalline complex becomes prolonged dried with 60 DEG C two hours. The water solubility of S (+) - ibuprofen amounts to 0.55 mg/ml for this product.

Example 4

Preparation of molecular entrapped S (+) - ibuprofens using 2,6-Di-0-methyl beta - cyclodextrin

450 ml waters become heated on 60 DEG C. 20.6 g (0.1 mol) S (+) - ibuprofens and 133.3 g (0.1 mol) 2,6-Di-0-methyl beta - cyclodextrin (DIMEB) bottom vigorous agitation added become. The obtained emulsion suspension mixture becomes with 600 RPM with 60 DEG C agitated. The integration procedure is terminated within approximately 24 hours. Subsequent one becomes the warm suspension on a warm glass filter in vacuo filtered. The product becomes prolonged dried with 60 DEG C two hours. S (+) - Ibuprofengehalt of the product amounts to 16.6%. The water solubility of S (+) - ibuprofen becomes on 21 mg/ml increased, which means one for instance 200fache increase of the solubility.

Example 5

Preparation of molecular entrapped S (+) - ibuprofens using a polymere hydroxyalkylierten Cyclodextrinderivates

20.6 g S (+) - Iboprofen and 300 g water-soluble Cyclodextrinpolymer (CDPS) become mixed into 400 ml waters with 60 DEG C. The reaction mixture becomes 10 hours prolonged agitated and subsequent spray-dried. S (+) - Ibuprofengehalt of the product amounts to 6.8%. The water solubility of S (+) - ibuprofen amounts to 8.0 mg/ml.

Example 6

Preparation water solubility using an ionic Cyclodextrinpolymeren, improved by S (+) - ibuprofens with

20.6 g S (+) - ibuprofens and 300 g of a Cyclodextrinpolymeren substituted by Diethylaminogruppen become mixed into 400 ml waters with 60 DEG C. The reaction mixture becomes two hours prolonged agitated and subsequent spray-dried. S (+) - Ibuprofengehalt of the product amounts to 6.8%.

Example 7

Preparation of S (+) - Ibuprofen Brausetabletten

< tb> < TABLE> Columns=2
< tb>
< tb> : 1 tablet contains in mg:
< tb> S (+) - Ibuprofen complex
< *>
from example 1 (corresponds 200 mg S (+) - ibuprofens) < SEP> 2065,0
< tb> Lactose< SEP> 700,0
< tb> Citronensäure< SEP> 150,0
< tb> Natriumdihydrogencitrat< SEP> 390,0
< tb> Natriumcarbonat< SEP> 125,0
< tb> Natriumhydrogencarbonat< SEP> 500,0
< tb> Magnesiumstearat< SEP> 40,0
< tb> Lemon flavour (company Dragoco, Nr.9/021907) < SEP> 0,8
< tb> Natriumcyclamat< SEP> 20,0

* The active substance content can become varied by 100 - 200 mg S (+) - ibuprofens per tablet. The adjuvants become corresponding reduced and/or. increased.

< tb> < /TABLE>

Example 8

Preparation of S (+) - Ibuprofen Brausetabletten

< tb> < TABLE> Columns=2
< tb>
< tb> : 1 tablet contains in mg:
< tb> S (+) - Ibuprofen complex
< *>
from example 4 (corresponds 200 mg S (+) - ibuprofens) < SEP> 1205,0
< tb> Lactose< SEP> 400,0
< tb> Citronensäure< SEP> 150,0
< tb> Weinsäure< SEP> 300,0
< tb> Natriumhydrogencarbonat< SEP> 375,0
< tb> Magnesiumstearat< SEP> 25,0
< tb> Lemon flavour (company Dragoco, Nr.9/021907) < SEP> 0,5
* The active substance content can become varied by 100 - 200 mg S (+) - ibuprofens per tablet. The adjuvants become corresponding reduced and/or. increased.

< tb> < /TABLE>

Example 9

Preparation of S (+) - Ibuprofen suspension

< tb> < TABLE> Columns=2
< tb>
< tb> : 100 g suspension contain:
< tb> S (+) - Ibuprofen Komplex< *> from example 1 (corresponds 2000 mg S (+) - ibuprofens) < SEP> 20.65 g
< tb> Sorbitol 70% - Lösung< SEP> 10.00 g
< tb> Natriumcyclamat< SEP> 0.40 g
< tb> Krauseminz flavor (hair man & Reimer 290057/89658) < SEP> 0.10 g
< tb> Methyl cellulose MHB 1000< SEP> 2.00 g
< tb> Sorbinsäure< SEP> 0.15 g
< tb> Cleaned Wasser< SEP> 66.70 g
< tb> < /TABLE>

Example 10

Preparation of S (+) - Ibuprofen syrup

< tb> < TABLE> Columns=2
< tb>
< tb> : 100 g syrup contain:
< tb> S (+) - Ibuprofen Komplex< *> from example 4 (corresponds 2.00 g S (+) - ibuprofens) < SEP> 12.05 g
< tb> Sorbitol 70% - Lösung< SEP> 14.30 g
< tb> Kirscharoma (hair man & Reimer 203816) < SEP> 0.02 g
< tb> Sorbinsäure< SEP> 0.15 g
< tb> Cleaned Wasser< SEP> 73.48 g
< tb> < /TABLE> EMI16.1 EMI17.1